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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,593	12/05/2001	Katherine S. Bowdish	1087-2	3532

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	PAPER NUMBER
1643	
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07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/006,593	BOWDISH ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11,18-23,36,44,85-87,89 and 96-126* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11,18-23,36,44,85-87,89 and 96-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/20/06;4/23/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The applicant has timely traversed the non-final rejection in the reply filed on 04/23/2007, and a response to the arguments is set forth.

2. Claims 4, 12-17, 24-35, 37-43, 45-84, 88 and 90-95 have been cancelled.

3. Claims 1, 44, 86, 96 and 99 have been amended.

4. Claims 113-126 have been newly added.

5. Claims 1-3, 5-11, 18-23, 36, 44, 85-87, 89 and 96-126 are under examination.

6. This office action consists of new grounds of rejections.

Rejections Withdrawn

7. The rejection of claims 1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89 and 96-112 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

8. The rejection of claims 1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89 and 96-112 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a NEW MATTER rejection. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of amendments to the claims.

9. The rejection of claims 1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89 and 96-112 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunoglobulin molecule or fragment thereof wherein one or more CDRs are replaced with: one EPO mimetic that binds to the erythropoietin receptor, one TPO mimetic that binds to the thrombopoietin receptor, both EPO mimetic or both TPO mimetics wherein the immunoglobulin molecule or fragment binds erythropoietin or thrombopoietin receptor respectively, does not reasonably provide enablement for an immunoglobulin molecule or fragment that comprises the number of replacement of a CDR with an EPO or a TPO or both EPO or both TPO peptide mimetics that do not bind either of the receptors OR an immunoglobulin wherein one or more amino acid residues of each of a CDR are replaced with one of the peptide mimetics is withdrawn in view of amendments to the claims.

Rejections Maintained

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1-3, 5-11, 18, 19, 22, 23, 36, 96, 99, 100, 101 and 104-112; and the newly added claims 113-126 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas et al (a) (WO 94/18221, published 8/94; cited in the previous office action mailed 10/18/2005) and further in view of Dower et al (WO 96/40750, published 12/96; cited in the previous office action mailed 10/18/2005) and Barbas et al (b) (PNAS 92:2529-2533, 1995; cited in the previous office action mailed 10/18/2005) and in view of Cwirla et al (Science, Vol, 276 13 June 1997; IDS 8.15.2005) and further in view of Wrighton et al. (Science. 1996. 273, 458-463) as evidenced by Helms (Protein Science. 1995, 4:2073-2081; cited in the previous office action mailed 08/20/2003) is maintained and made here within.

The applicant argues that the references taken alone of in any combination, fail to teach or suggest an immunoglobulin molecule, or fragment thereof wherein an agonist peptide replaces a single portion of a CDR and wherein the immunoglobulin or fragment thereof binds to and agonizes a receptor as claimed (page 11 of the response filed on 04/23/2007).

In response to the above arguments, the applicant is reminded that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally

available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Please see below for a detailed explanation.

In particular, the applicant argues that Barbas (a) teaches methods for designing and using CDR replaced antibody molecules for in vivo use as a therapeutic reagent for blocking on inhibiting and Barbas (b) discloses anti-tetanus toxoid Fab molecules that are CDR replaced and bind to DNA and such antibodies do not even bind to a receptor let alone suggest that such antibodies could be used to agonize receptor activity (page 11 of the response filed on 04/23/2007). Further, applicants argue that Cwirla and Wrighton are directed towards the discovery of small peptides that can be used as agonists of the EPO and TPO receptor, and not tested for receptor agonist activity in the context of the phage display (page 12 of the response filed on 04/23/2007). Thus, the applicant argues that one of ordinary skill in the art would not be motivated to incorporated the small agonist peptides into the CDR replaced antibodies of Barbas (a) or (b).

The above arguments are carefully considered, but are not found persuasive. The applicants are again reminded of the teachings of the previously cited art wherein, Barbas et al (a) teach replacing CDRs in a heavy or light chain of an antibody or Fab fragment with biologically active peptides, Barbas (b) teach such replacement of CDRs can be carried out in the anti-tetanus toxoid antibody, Cwirla teaches that a TPO peptide (which is 100 % identical to the TPO peptide of the instant application) that can

act as a potent agonist of the TPO and as a potent natural cytokine, Wrighton et al teach small EPO peptide mimetics that bind to and activate the receptor for the cytokine EPO and show that the peptides act as agonists and stimulate erythropeoiesis in mice.

Thus, by combining the teachings of Barbas (a), Barbas (b), Cwirla and Wrighton, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have replaced CDRs in a heavy or light chain as taught by Barbas (a) of an anti-tetanus toxoid antibody as taught by Barbas (a) with a TPO agonistic peptide as taught by Cwirla et al or an EPO agonistic peptide as taught by Wrighton et al.

The applicants argument in regard to Barbas (a) teaching the inhibition or antagonizing functions of the antibody is noted, however not persuaded. The purpose of the Barbas (a) reference is to show that the method of replacing CDRs in a heavy or light chain of an antibody or Fab fragment with biologically active peptides was known at the time of the invention. The functions of the antibodies produced by the method of Barbas (a) are irrelevant. Barbas (a) teaches the method of replacing CDRs with biologically active peptides; and since Cwirla and Wrighton et al teach EPO and TPO mimetics (interpreted as biologically active peptides), it would have been obvious to one of ordinary skill in the art to have produced an antibody molecule with EPO or TPO peptide mimetics in place of CDRs.

It is noted that the applicant states (page 12, 2nd paragraph in particular).

> "Cwirla and Wrighton are directed to the discovery of *small peptides* that can be used as agonists of the EPO or TPO receptor; and In particular, Wrighton notes that "[t]his discovery may form the basis for the design *of small molecule* mimetics of EPO" and that *"small molecule* EPO mimetics may have desirable pharmacological properties such as oral bioavailability or the ability to be delivered trans-dermally" (see page 463, emphasis

> added). Why would one of skill in the art want to incorporate the peptides of, for example, Wrighton, into a much larger antibody molecule when Wrighton teaches that the goal is develop small molecule therapeutics for their desirable pharmacological properties? This would be doing exactly the opposite of the teachings of Wrighton"

In response to the above statement, one would not focus away from combining the previously cited art, instead would be motivated because one of ordinary skill in the art would have been motivated to introduce the peptide mimetics taught by Cwirla and Wrighton into the anti-tetanus toxoid antibody as taught by Barbas (b) into CDRs in a heavy or light chain as taught by Barbas (a), because it is well known in the art that peptides generally have very short serum half-lives and additional modifications are often required to be therapeutically effective *in vivo and* such modifications may alter the peptide activity or safety profile. In addition, one would be motivated and would have had reasonable expectation of success to increase the half-life of an agonist peptide by grafting into a human antibody framework CDRs.

The applicants points out (page 12 of the response filed 04/23/2007) that Helms reference discusses stability and conformational effects of the introduction of sequences into CDR regions and suggests that the introduction of novel sequences into CDRs can significantly *diminish the stability* of immunoglobulins ... Helms teaches away from the claims as currently pending.

While Helms et al discuss that stability and conformational effects of the introduction of sequences into CDR regions and suggests that the introduction of novel sequences into CDRs can significantly diminish the stability of immunoglobulins; the reference is cited in association with the claims (in particular claim 2 and 3 etc.,) wherein the at least one flanking sequence is included (for example having atleast one

proline) that is covalently linked to the peptide mimetic. Thus, the studies of Helms et al further support and read on the instantly claimed invention wherein not just a CDR sequence can be introduced, but a flanking sequence covalently linked to the CDR sequence should be introduced into the CDR positions of the anti-tetanus toxoid antibody as taught by Barbas (b).

The applicant is further reminded that a skilled artisan would be motivated to replace the CDRs with biologically active peptides as taught by Barbas (a), wherein the biologically active peptides can include EPO or TPO mimetics as taught by Cwirla and Wrighton, which are small agonist peptides. Furthermore, since Wrighton discloses that such small agonist peptides have desirable pharmacological properties in addition to Dower et al who teach that the TPO peptides can be used for therapy and as stated earlier peptides generally have very short serum half-lives and additional modifications are often required to be therapeutically effective *in* vivo; *one* would be motivated and would have had reasonable expectation of success to introduce the EPO or TPO mimetics taught by Cwirla and Wrighton into the anti-tetanus toxoid antibody as taught by Barbas (b) into CDRs in a heavy or light chain as taught by Barbas (a) for therapeutic purposes.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

New Grounds of Rejections

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. The rejection of claims 1-3, 5-11, 18, 19, 22, 23, 36, 44, 85-87, 89 and 96-112; and the newly added claims 113-126 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunoglobulin molecule or fragment thereof comprising a CDR wherein a TPO mimetic replaces a single CDR, wherein the immunoglobulin molecule or fragment thereof binds to and agonizes TPO receptor does not reasonably provide enablement for an immunoglobulin molecule or fragment thereof comprising a CDR wherein a TPO mimetic replaces a single portion of said CDR, wherein the immunoglobulin molecule or fragment thereof binds to and agonizes TPO receptor.

Thus, the claims still recite an immunoglobulin molecule or fragment thereof wherein portions of CDRs are replaced with a mimetic. Thus, the claims as written comprise an immunoglobulin wherein the CDRs consist of substitution of any number of amino acids (ranging from one amino acid to the entire length of the CDR) with a peptide mimetic. The specification teaches replacement of CDRs with the EPO and TPO sequences (see Examples 3 and 5), but does not enable immunoglobulin or antigen fragment thereof wherein one or more amino acid residues of each of two CDRs are replaced with a peptide mimetic.

The instant specification shows the replacement of the entire anti-tetanus toxoid Fab heavy chain CDR3 with a TPO peptide (example 1), wherein the peptide mimetic is flanked by two amino acids at the N and C-terminus using the NNK doping strategy.

Further, the replacement of HCDR2, LCDR1, LCDR2 and LCDR3 with a TPO peptide in a similar fashion is disclosed in examples 2 and 3. Also, the replacement of HCDR3 with an EPO mimetic peptide with two flanking amino acids at N and C-terminus is described in example 5.

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation off the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results.

Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol 79 page 1979) teach that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRS, may dramatically affect antigen-binding function. Rudikoff et al. also teach that the alteration phosphocholine-binding function of a single amino acid in the CDR of a myeloma protein resulted in the loss of antigen-binding (please see the entire document, in particular)

Further, Colman et al (Research in Immunology 1994, 145:33-36) teach the specificity of antibody-antigen interaction, wherein in one structural context, a very conservative substitution may abolish binding; in another, a non-conservative substitution may have very little effect on the binding affinity. Current estimated of the potential number of antibody molecules that can be generated by all the known genetic mechanisms is in excess of 10^{18}. This and similar other estimates assume each of the 20 amino acids is different from every other amino acid, which is appropriate for

purpose of enumeration but not for the purpose of estimating how many different antibody specificities can be produced by an animal (page 35, in particular).

In addition, Ibragimova and Eade (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198) teach that factors affecting protein folding and stability are governed by many small and often opposing effects and that even when the "rules" are know for altering the stability of a protein fold by the introduction of a single point mutation the result is not reliable because the balance of forces governing folding differs for different protein sequences, and that the determination of the relative magnitude of the forces governing the folding and stability of a given protein sequence is not straightforward (page 2191, first column, lines 12-17 and second column, lines 3-8).

Thus, the specification teaches the replacement of the complete CDR sequences with the TPO or EPO mimetic peptides that are flanked with two amino acids on either side. The specification does not disclose the replacement of a single portion of a CDR, which can be interpreted as one or more amino acids within the CDR region, with teither a TPO or an EPO mimetic peptide. Further, the specification is completely silent in regard to the substitution of HCDR1.

The claims are drawn to an immunoglobulin molecule comprising the replacement of CDRs and hence the structural integrity of the CDRs is considered important for the functionality of such immunoglobulin molecule. A skilled artisan would not be able to practice an immunoglobulin molecule wherein one or more amino acids within CDRs are replaced with a TPO mimetic peptide, without undue experimentation.

Hence, in view of the lack of guidance, lack of examples, and lack of

predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-3, 5-8, 18, 22, 23, 36, 44, 85, 97, 98, 99 and 100-112 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 4, 5, 6, 8, 10, 11, 16, 26-35, 38-56 of copending Application No. 10/307,724.

The applicants argue that the provisional rejections made under the judicially created doctrine of obviousness-type double patenting be held in abeyance until

otherwise allowable subject matter is identified in the instant application. Once allowable subject matter has been identified, Applicants will evaluate the filing of a terminal disclaimer or providing arguments in view of the claims pending at that time (page 15 of the response filed on 04/23/2007).

The above arguments are carefully considered, but are not found persuasive because claims of copending Application No. 10/307,724 are still pending. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Thus, claims 1-3, 5, 6, 7, 8, 18, 22, 23, 36, 44, 85 and 97-112 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 4, 5, 6, 8, 10, 11, 16, 26-3 and 38-56 of copending Application No. 10/307,724.

Conclusion

16. No claims are allowed

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER